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10/506,962	04/19/2005	Axel Ullrich	WEICKM-0041	6941

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,962	ULLRICH ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *5-7,11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-12 are all the pending claims in this application.

Election/Restrictions

2. Applicant's election with traverse of Group I (Claims 1-10) in the reply filed on 10/29/07 is acknowledged. Applicants have not provided any technical or legal arguments why the restriction is improper. The claims do not satisfy unity of invention under § 1.475: each group lacks unity with each other group because there is no single general inventive concept specifically describing the unique special technical feature in each group. This is because the instant claims do not recite one common or corresponding special technical feature(s) that define the contribution which each claimed invention of Groups I and II , considered as a whole, makes over the prior art (see Cohen cited in the Office Action of 9/28/07). Applicants have not addressed this aspect of the Examiner's determination insofar as whether the claimed technical feature is a contribution over Cohen.

Applicants argue that the Examiner has not demonstrated an undue burden to examine all groups.

Applicants are reminded that an Examiner is not required to establish a search burden in finding lack of unity much less where a lack of unity restriction is required. Chapter 1800 of the MPEP does not speak to this issue.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 11 and 12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or

linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/29/07.

4. Applicant's election with traverse of species for compound affecting a growth factor receptor ligand precursor in the reply filed on 10/29/07 is acknowledged. The traversal is on the ground(s) that the Office has not set forth characteristics of the claimed species of compounds that are mutually exclusive.

This is not found persuasive. The specification defines three non-overlapping and non-obvious targeting substrates for compounds which are not structurally or functionally related, for example on pp. 3-4: CMR197 or an antibody for a growth factor receptor ligand precursor; batimastat (BB-94), marimastat, TAPI and TIMP-1-2-3 or -4, particularly TIMP-3 for a metalloproteinase; and Ag1478 or an antibody for EGFR.

The requirement is still deemed proper and is therefore made FINAL.

5. Claims 5-7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected species of compounds, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/29/07.

6. Claims 1-4 and 8-10 are all the pending claims under examination.

Information Disclosure Statement

7. The information disclosure statement filed 9/8/04 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other

information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Specification

8. The disclosure is objected to because of the following informalities:

The guidelines under 37 CFR 1.77(b) illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

a) The specification is objected to for failing to provide a cross-reference to the priority documents for this application.

b) The Brief Description of the Drawings on p. 9 should be inserted between the Summary of the Invention and the Detailed Description of the Invention.

c) The Abstract of Disclosure is a virtual copy of the abstract from the corresponding WO reference and should appear as a separate sheet to the specification.

d) The figure legends for Figures 1-7 are objected to because they do not describe in brief but sufficient detail the data depicted in any of the figures.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims 1-4 and 8-10 are directed to non-statutory subject matter.

Claims 1-4 and 8-10 are "use" claims. Applicants are required to cancel the claims or amend the claims into what is otherwise interpreted as a method of use, e.g., which according to the Office Action of 9/28/07 is interpreted as a method of preventing or treating a process associated with a disorder with increased G-protein mediated signal transduction using a compound which inhibits the activation of a growth factor receptor of the EGFR family.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-4 and 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1-4 and 8-10 recite improper Markush group language: "selected from". See MPEP 803.02 for proper Markush group language.

b) Clams 3 and 4 are indefinite for the recitation "acts on" in Claim 3 because it is not clear what the meaning of the action is more especially in reference to Claim 1 which requires that the compound inhibit activation. It is not clear if in requiring that the compound "act on" the substrate that it requires some aspect of activation, in order for the compound to inhibit activation of a growth factor receptor.

c) Claim 8 recites the limitation "the agent" in reference to the compound. There is insufficient antecedent basis for this limitation in the claim.

d) Claim 8 is indefinite for the recitation that "the agent" is "a pharmaceutical composition" when more generally a composition is considered to comprise an agent (or a substance or a compound). The term "agent" signifies a single kind of molecule that would necessarily exclude other materials within the composition. It is not even clear how one of skill in the art could technically produce an agent comprising the composition, whereas the pharmaceutical composition could comprise the agent and pharmaceutically acceptable additives.

e) Claim 10 recites the limitation "the cancer". There is insufficient antecedent basis for this limitation in the claim and in Claim 1 from which the claim depends.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

11. Claims 1-4 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, because while being enabled from the prior art for a method of effecting cell lines in vitro or treating an in vivo animal cancer model with a growth-factor receptor ligand precursor inhibitor for pro-HB-EGF such as CRM197 or an anti-pro-HB-EGF antibody, does not reasonably provide enablement for preventing or treating any disorder including any cancer much less any human cancer with any compound that inhibits any growth-factor receptor ligand precursor much less pro-HB-EGF or any pro-HB-EGF-like ligand. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence

or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention

Claims 1-4 and 8-10 are interpreted as being drawn to a method for preventing or treating a process selected from cell proliferation, cell migration, invasivity and anti-apoptosis in a disorder which is associated with increased G-protein mediated signal transduction comprising use of a compound which inhibits the activation of growth factor receptor of the EGFR family (Claim 1) where the receptor is EGFR (Claim 2) and the compounds acts on a growth-factor receptor ligand precursor (Claim 3) and where the growth-factor receptor ligand precursor of Claim 3 is EGF or EGK-like protein (Claim 4) and where the agent is formulated into a pharmaceutical composition (Claim 8) and where the disorder of Claim 1 is cancer (Claim 9) and the cancer is a human cancer (Claim 10).

Disclosure in the Specification

The specification contemplates using CMR197 (binds to pro-HB-EGF) or an antibody capable of binding to pro-HB-EGF as the only embodiments for compounds which would effect a growth-factor receptor ligand precursor. The specification contemplates using CMR197 of the antibody in order to treat *or* prevent a disorder associated with G-mediated signal transduction effecting EGFR where the agent effects a process of cell proliferation, cell migration, invasivity and/or anti-apoptosis. No where in the specification are any methods using an in vitro cell-based assay much less an

animal model correlate for any disorder encompassed by the claims showing that either one of the compound or the antibody could be practiced in the claimed method and that a prevention or treatment effect would be accomplished.

Prior Art Status: Cancer Treatment and Prevention is Unpredictable

In vitro drug testing *may be* a platform technology in a determination of enablement, but the complexity and difficulty of in vivo cancer treatment is underscored by Voskoglou-Nomikos (Clin. Can. Res. 9:4227-4239 (2003)). Voskoglou-Nomikos conducted a study using the Medline and Cancerlit databases as source material in comparing the clinical predictive value of three pre-clinical laboratory cancer models: the in vitro human cell line (Figure 1); the mouse allograft model; and the human xenograft model (Figures 2 and 3). Significantly when each of the cancer models was analyzed against Phase II activity, there was a negative correlation for the in vitro human cell line models being predictive of good clinical value. No significant correlations between preclinical and clinical activity were observed for any of the relationships examined for the murine allograft model. And the human xenograft model showed good tumor-specific predictive value for NSCLC and ovarian cancers when panels of xenografts were used, but failed to predict clinical performance for breast and colon cancers. Voskoglou-Nomikos suggests that "the existing cancer models and parameters of activity in both the preclinical and clinical settings may have to be redesigned to fit the mode of action of novel cytostatic, antimetastatic, antiangiogenisis or immune-response modulating agents" and "New endpoints of preclinical activity are

contemplated such as the demonstration that a new molecule truly hits the intended molecular target" (p.4237, Col. 1, ¶6).

Dennis (Nature 442:739-741 (2006)) also recognizes that human cancer xenograft mouse models for testing new drugs has been and will remain the industry standard or model of choice, but it is not without problems because "many more [drugs] that show positive results in mice have little or no effect in humans" (p. 740, Col. 1, ¶3). Dennis describes transgenic animal mouse models as an alternative to xenograft modeling and the general differences between mice and humans when it comes to tumor modeling: 1) cancers tend to form in different types of tissue, 2) tumors have fewer chromosomal abnormalities, 3) ends of chromosomes (telomeres) are longer, 4) telomere repairing enzyme active in cells, 5) short lifespan, 6) fewer cell divisions (10^{11}) during life than humans (10^{16}), 7) metabolic rate seven time higher than humans, and 8) lab mice are highly inbred and genetically similar. One skilled in the art would reasonably conclude that evidence obtained in mouse xenograft models would not correlate with results expected in human tumors.

Skill in the Art/Undue Experimentation

It appears that undue and inordinate experimentation would be required of one skilled in the art to practice the instant invention using the teachings of the specification alone and the specification fails to enable the use of the method for tumor therapy and tumor prevention much less in any human. Due the unpredictability of cancer therapeutics in general, as evidenced by the results from Voskoglou-Nomikos' study comparing animal model correlates to human diseases, and based on Dennis

appreciation of clontypic cell based systems, *and* in view of the insufficient guidance and working examples concerning the use the claimed growth-factor receptor ligand precursor inhibitor, one skilled in the art would not know how to practice the broadly claimed invention. One skilled in the art could not administer to any subject having any disorder any growth-factor receptor ligand precursor inhibitor for the treatment and/or prevention of any disorder much less a human cancer and its accompanying pathologies, without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

CRM197 (or Diptheria toxin): HB-EGF inhibitor

12. Claims 1-4 and 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Prenzel et al. (Nature 402(6764):884-8 (1999)).

The interpretation of Claims 1-4 and 8-10 is discussed supra. The claims are most reasonably interpreted as being drawn to a method of treatment.

Prenzel discloses that CRM197, a non-toxic mutant of diphtheria toxin, inhibits strongly and specifically the mitogenic activity of HB-EGF. CRM197 pretreatment completely inhibited tyrosine phosphorylation of the EGFR induced by GPCR agonists LPA and carbachol as well as TPA in COS-7 cells (Figure 3B). EGF-induced receptor tyrosine phosphorylation was unaltered showing specificity of CRM194 for the growth-factor receptor ligand precursor (p. 886, Col. 1, ¶3-4). Prenzel extends the observations to the pathophysiological relevance of EGFR transactivation through G-protein mediated growth factor precursor processing in human prostate cancer (p. 888, Col. 1, ¶3).

13. Claims 1-4 and 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Freeman et al. (J. Cell. Biochem. 68:328-338 (1998)).

The interpretation of Claims 1-4 and 8-10 is discussed supra.

Freeman discloses HB-EGF is of potential interest in prostatic disease because of its role as a connective tissue and tumor cell growth factor and also because of the on-going searches for cell-surface molecules that mght potentially be used as targets for drug delivery in therapy for prostatic diseases (p. 329, Col. 2, ¶2). Freeman teaches pro-HB-EGF binds diptheria toxin (DT) and that LNCaP (human prostate adenocarcinoma cell line) which express pro-HB-EGF and when exposed to (DT) is specifically inhibited in protein synthesis (p. 333, Col. 2, ¶2; figure 5).

14. Claims 1-4 and 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Bevec (WO 200135899; published May 25, 2001).

The interpretation of Claims 1-4 and 8-10 is discussed supra.

Bevec discloses compounds for treating Helicobactor induced diseases such as mucosa-associated lymphoid tissue lymphoma and intestinal-type adenocarcinoma (p. 3, lines 17-20) using pro-HB-EGF inhibitors (p. 8, line 6-10) such as CRM197 (p. 16, line 14-17; p. 19, lines 6-9). Bevec shows that addition of CRM197 to human gastric cancer cell lines in vitro could block H. pylori-induced production of IL-8 by 25% (p. 19, lines 16-22; and Figure 4).

Anti-HB-EGF Antibody inhibitor

15. Claims 1-4, 8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Ito et al. (BBC 1310(1): 163-167 (1996); Abstract).

The interpretation of Claims 1-4, 8 and 9 is discussed supra.

Ito discloses that a bioactive HB-EGF-like protein stimulates DNA synthesis in EP170.7 cells, which are derived from 32D cells, a murine IL-3-dependent myeloma cell line. Addition of an anti-HB-EGF antibody neutralizes the mitogenic effect of the HB-EGF protein on the cell line.

16. Claims 1-4 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Elder et al. (US 20020169176; published November 14, 2002; filed February 11, 2002).

The interpretation of Claims 1-4 and 8-10 is discussed supra.

Elder discloses a goat polyclonal antibody to HB-EGF that neutralizes HB-EGF activity in Balb/3T3 cell proliferation assays. Elder discloses organ cultures of adult human skin were treated for 8 days with retinoic acid (RA) and concomitantly with the neutralizing antibody to HB-EGF or normal goat serum, and that the anti-HB-EGF inhibited RA-induced changes such as hyperplasia.

17. Claims 1-4 and 8-10 are rejected under 35 U.S.C. 102(e) as being anticipated by Hanke et al. (WO 200077195; published December 21, 2000).

The interpretation of Claims 1-4 and 8-10 is discussed supra.

Hanke discloses the protein for HB-EGF and antibodies (p. 8, lines 6-8) and pharmaceutical compositions comprising the anti-HB-EGF antibody and used in the treatment of disorders having HB-EGF-mediated associated with cell proliferation and which include human cancers (p. 8, lines 17-34)

Conclusion

18. No claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

/Larry R. Helms/
Supervisory Patent Examiner